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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/513,151	02/25/2000	Siegfried Hekimi	979-1-017	7817

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/513,151	HEKIMI ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-24,29,30,33,34 and 39* is/are rejected.

7)☒ Claim(s) *25-28,31,32 and 35-38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/2.003
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 23, 25, 27 and 29 have been amended. Claims 30-39 have been added. Claims 21-39 are pending and under consideration.

The rejection of claims 23 and 24 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record. Claims 31-39 are also rejected for the same reasons of record. Claim 23 is drawn to a fragment of the polynucleotides of SEQ ID NO:3 or a fragment of the polynucleotides encoding SEQ ID NO:3 or the complement thereof, wherein said fragment can rescue at least one phenotype in a gro-1(e2400) c elegans mutant. Claim 24 is drawn to the fragment of claim 24 comprising nucleotides 1121-1210 of SEQ ID NO:3 wherein a polypeptide encoded by said fragment contains a zinc finger motif. The specification as filed disclosed that the C elegans gene of gro-1 was able to rescue the e2400 mutant (page 17, lines 11-32). Figure 9 indicates that the human version of the C elegans gene is hgro-1 (SEQ ID NO:3). The specification does not provide support for amendments substituting functions of human hgro-1 (SEQ ID NO:3) polynucleotide for functions of the C elegans gro-1(SEQ ID NO:2) as it was not demonstrated by the specification as filed that the fragments of the human hgro-1 gene can substitute for the C elegans gene in the rescue of the e2400 mutant phenotype. With regard to fragment of SEQ ID NO:3 that can suppress at least one 2400 phenotype, it is noted that the specification as originally filed teaches cosmid which can rescue the e2400 phenotype (figure 2A), the subcloning of the region common to the rescuing cosmids to pMQ2 which appeared to contain two genes, the first of which, when subcloned as pMQ3 (ZC395.7) was unable to rescue said phenotype. The specification then identified the remaining gene as gro-1 (page 9, line 12 to page 11, line 4). The specification did not contemplate a subregion of gro-1 or hgro-1 that would rescue the e2400 phenotype. This is insufficient support for amendments drawn to fragments which can rescue the e2400 phenotype. Claim 23 specifies the rescuing of "at least one" phenotype in a gro-1 C. elegans mutant. There is no support in the specification for the suppression of one characteristic of the 2400 phenotype versus the suppression of all the characteristics. The specification as filed does not provide

enablement for the use of that different elements of the gro-1 gene for the suppression of different 2400 phenotypes. Further, newly added claims 23 and 24 are dependent on the complement of SEQ ID NO:3 or the complement of the polynucleotides encoding the polypeptide of SEQ ID NO:3, and the specification as filed provides no support for an anti-sense construct of gro-1 or hgro-1 which can rescue the phenotype of the e2400 mutant.

Applicant argues that it is not necessary to disclose what is conventional or well known in the art and that one of skill in the art would recognize that applicants contemplated subclones comprising only a fragment of the gro-1 gene. This has been considered but not found persuasive. Subfragments of the gro-1 gene are not "conventional in the art". Without a specific contemplation of a fragment of SEQ ID NO:3, one of skill in the art would not recognize that said fragment can recognize the gro-1 phenotype. Applicant argues that the skilled person would have understood that the cosmid clones contained random fragments of the C elegans genome and that one end of a cosmid or its subclones may lie within the gro-1 gene, This has been considered but not found persuasive. The claims are drawn to a fragment of a polynucleotide that encodes a polypeptide comprising the amino acid encoded by the nucleotide sequence of SEQ ID NO:3 (degenerate coding sequence), and not a fragment of a cosmid clone.
Applicant argues that the human gro-1 gene was obtained by assembling fragments of hgro-1 genes, and that the C elegans rescue assays were well known at the time of filing. This has been considered but not found persuasive. This is not a rejection based on lack of enablement. The specification lacks adequate written description of said fragments of SEQ ID NO:3 and fragments of degenerate coding sequence of SEQ ID NO:3, wherein said fragments can rescue the gro-1 C elegans mutant.

The rejection of claims 21-24 under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility, and under 35 U.S.C. 112, first paragraph, is withdrawn in light of applicant arguments to the fact that the instant SEQ ID NO:3 is a human isopentenyl transferase, and thus an enzyme.

The rejection of claim 22 under 35 U.S.C. 102(b) as being anticipated by Hudson (Accession number G24438, May 31, 1996). Claim 22 is drawn in part to a complement of a polynucleotide

that encodes a polypeptide encoded by SEQ ID NO:3 is maintained for reasons of record. Hudson et al discloses human STS WI-12773 which is a complement to residues 1778-2029 of SEQ ID NO:3. Applicant argues that Hudson et al do not disclose a nucleic acid which encodes a polypeptide comprising the amino acid sequence encoded by SEQ ID NO:3. This has been considered but not found persuasive. Claim 22 is drawn in part to the complement of said polynucleotide and does not specify that the complementary region need encode a polypeptide, not be a full-length complement.

Claims 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by BioLabs Catalog (1993-1994, page 91). Claim 21 is drawn in part to a complement of SEQ ID NO:3; claim 22 is drawn in part to a complement of a polynucleotide that encodes a polypeptide encoded by SEQ ID NO:3. BioLabs Catalog disclose random hexamers which are complements of the aforesaid polynucleotides. Neither claim specifies that the complements must be full-length complements.

The rejection of claims 23 and 24 under 35 U.S.C. 102(b) as being anticipated by Bonaldo et al (Genome Research, 1996, Vol. 6(9):791-806) as evidence by accession number BM721352 is withdrawn in light of applicant arguments..

Claims 29, 30, 33, 34, and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated host cells comprising vectors, does not reasonably provide enablement for host cells comprised within a transgenic animal, or an animal or human being having been treated by gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
When given the broadest reasonable interpretation, claims drawn to host cells encompass host cells within a patient having received gene therapy, or within a transgenic animal. The specification is not enabling for these uses for the following reasons:

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well

developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that the level and consistency of expression of

transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

The specification does not provide guidance in the making of host cells within a transgenic animal comprising the instant recombinant polynucleotides. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. The vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriate regulatory regions (Houdebine, Journal of Biotechnology, 1994, Vol. 34, pp. 269-287, see bridging pages 272-273) and expression is heavily dependent on the site of integration in the host genome, and the site of integration is presently unpredictable (Houdebine, page 277, column 1). Therefore, it is concluded that one of skill in the art would undergo undue experimentation in order to make the instant recombinant polynucleotides and cells within a transgenic animal.

Claims 25-28, 31, 32, 35-38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
6/14/2004

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER